The Pharmacology of Ethyl Chloride.

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(From the Physiological Laboratory of the University of Melbourne.)

The rapidity with which ethyl chloride has established its claims as a general anæsthetic for short operations appears justified by the advantages which its employment offers. It induces anæsthesia pleasantly and very rapidly, and compares favourably with nitrous oxide in these respects. The rapidity with which anæsthesia is induced, and the comparatively prompt recovery upon cessation of the administration, combined with the relatively small degree of vomiting or nausea, are its great advantages over ether and chloroform. The greater duration of anæsthesia following upon cessation of administration together with its portability are its advantages over nitrous oxide. Its position, therefore, in the armamentarium of the anæsthetist is that of filling the important gap between the light and brief anæsthesia of nitrous oxide and the deep narcosis of chloroform or ether.

This position is held, however, not without disabilities. In the first place muscular relaxation is not often completely attained until a deep degree of narcosis is reached and, more important by far, it is not as safe as nitrous oxide. The death rate is much greater than that of nitrous oxide and according to McCardie (1), is as high as 1 in 3000.

Ethyl chloride was first used as a general anæsthetic in 1848 by Heyfelder. Benjamin Ward Richardson experimented with it in 1867 and it was the subject of an enquiry by a Committee of the British Medical Association in 1880, who reported unfavourably upon its employment as a general anæsthetic. The revival of ethyl chloride as an anæsthetic for short periods occurred in 1895—6 and an historical account of its re-introduction will be found in a paper, "Ethyl Chloride as a General Anæsthetic," by W. J. McCardie (2). According to McCardie some experimental observations upon its pharmacological action have been made by Wood and Cerna, Koenig, Malherbes, and Roubinovitch, but I regret that the literature has not been available, and I have been unable to consult these papers.

The physiological action of a commercial preparation containing ethyl chloride 65 per cent., methyl chloride 30 per cent., and ethyl bromide

5 per cent., sold under the name of "Somnoform," was investigated by Cole (3).

Cole's experiments were performed for the most part upon rabbits, but in three cases cats were used. The quantity of Somnoform in the air inspired was not ascertained. Cole found the effect upon the respiration to be at first stimulative, followed, when large doses were employed, by standstill of the respiration, with the diaphragm in a condition of tonic contraction. The changes in the circulation were increased rate and diminished power of cardiac contractions and gradual fall of blood-pressure. No effect upon the vaso-motor system was discovered. The vagus endings in the heart were paralysed.

Interesting clinical observations have been reported by McCardie (1), Hewitt (4), and others.

McCardie's papers are particularly valuable, as, besides detailing the results of an extensive personal experience with this anæsthetic, he has collected as far as possible the experience of others at home and on the Continent.

The present paper records the results of work undertaken with a view to studying the pharmacology of ethyl chloride, in the hope that this might be of some value to those who may be concerned with its administration, and with the view of saving what appears to me to be a valuable anæsthetic agent from coming under the suspicion of being unduly dangerous.

For better comparison with the effects of chloroform, which have been frequently studied, dogs were used in all of the experiments, since these animals have been generally employed in chloroform research. In all experiments morphine and ether were used as the preliminary anæsthetics.

The Solubility of Ethyl Chloride in Water and Blood.

Ethyl chloride vapour I find to be soluble in water to the extent of 253·36 per cent. by volume (0·678 per cent. by weight) at 21° C. and at 760 mm. I have also ascertained the extent of its absorption by blood. There was considerable difficulty in determining this in consequence of the blood becoming of a tarry consistence as the absorption increased. In this condition the absorption progressed very slowly; for instance, in one experiment in which 100 c.c. of blood was employed and 496 c.c. of ethyl chloride vapour had already been absorbed, it required eight hours' contact, with continual shaking, for absorption of a further 5 c.c. In consequence of this physical difficulty, the complete absorptive power of blood for ethyl chloride was not determined. It is only possible to state that blood at 38° C. takes up an amount exceeding 500 per cent. by volume of the vapour.

The determinations were made in a special absorptiometer, which was kept at constant temperature by means of a water-bath, and in which arrangements were made for continuous shaking of the bulb containing the water or blood respectively. The bulb communicated by means of a narrow-bored tube with a gas burette containing the vapour of ethyl chloride. Measured quantities of vapour were passed into the bulb from time to time as absorption progressed, and the actual quantity taken up determined. The pressure in the absorptiometer was maintained constant by a variable mercury level.

In these determinations the blood was found to lake in the earlier part of the absorption process, but no massive formation of hæmoglobin crystals occurred as in the case of chloroform under like conditions. Blood absorbs more than twice as much of the gas as water under similar conditions. Ethyl chloride, like chloroform, evidently enters into chemical union with the blood.

Effect of Ethyl Chloride upon the Heart Isolated from the Central Nervous System.

In a previous investigation (5) of the effect of chloroform upon the isolated heart the method of Hering was employed. As, however, some difficulty is apt to happen in this method in consequence of the tendency to the formation of clots in the U-cannula when the blood-pressure falls, I have devised the following method, by means of which a circuit is maintained without the introduction of foreign bodies, such as cannulæ, for establishing continuity.

It consists in the ligation of all of the arterial trunks except the left subclavian, the aorta being tied just beyond the left subclavian artery. The ascending branches of the left subclavian and the vertebral arteries are then tied. One of the carotid arteries was used for recording the blood-pressure. The vagi were divided. The blood supply to the central nervous system was thus cut out and the operation of the central nervous system was in this way abolished. The heart circulated normal arterial blood.

In experiments under the above conditions, in which simultaneous blood-pressure curves and plethysmographic records of the changes in the volume of the left leg were taken under chloroform narcosis, it was found that the changes in the blood-pressure were accompanied by corresponding changes in the volume of the foreleg (left) in which the circu ation was affected.

Definite mixtures of ethyl chloride and air were administered by artificial respiration from a gasometer in which the mixture was contained. The Cambridge Scientific Instrument Company's apparatus was used for artificial respiration.

The experiments, records of which appear in figs. 1, 2, 3, and 4, demonstrate the gradually-increasing effects upon the isolated heart of varying percentages of ethyl chloride in the air inspired.

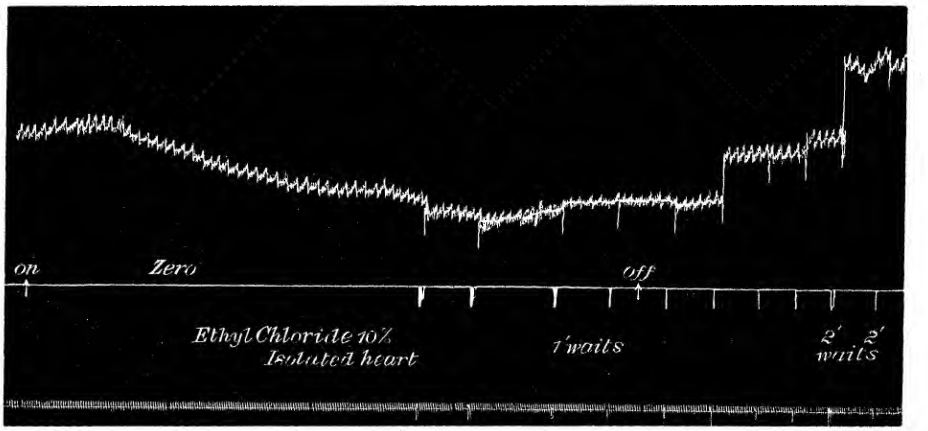

FIG. 1.—$\frac{3}{4}$ size of original.

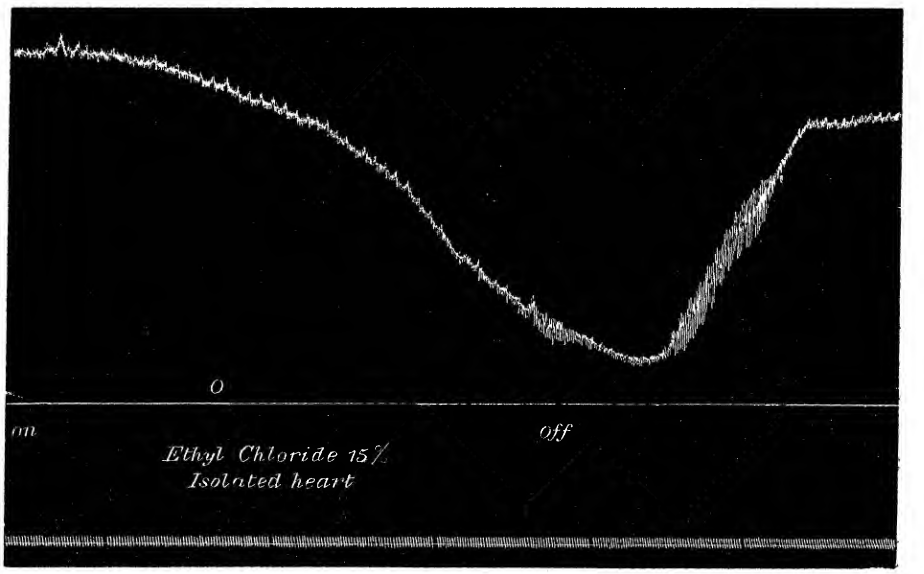

FIG. 2.—$\frac{3}{4}$ size of original.

The effect upon the work done by the heart was as follows :—

Expt.	1.	10	p.c.	ethyl	chloride	administered.	Blood-press. fell	from 92 to 58	mm. Hg in 8′ 15″
,,	2.	15	,,	,,	,,	,,	,,	158 ,, 63	,, 3′ 12″
,,	3.	20	,,	,,	,,	,,	,,	160 ,, 72	,, 1′ 1″
,,		20	,,	,,	,,	,,	,,	160 ,, 62	,, 0′ 59″
,,	4.	30	,,	,,	,,	,,	,,	164 ,, 34	,, 0′ 46″

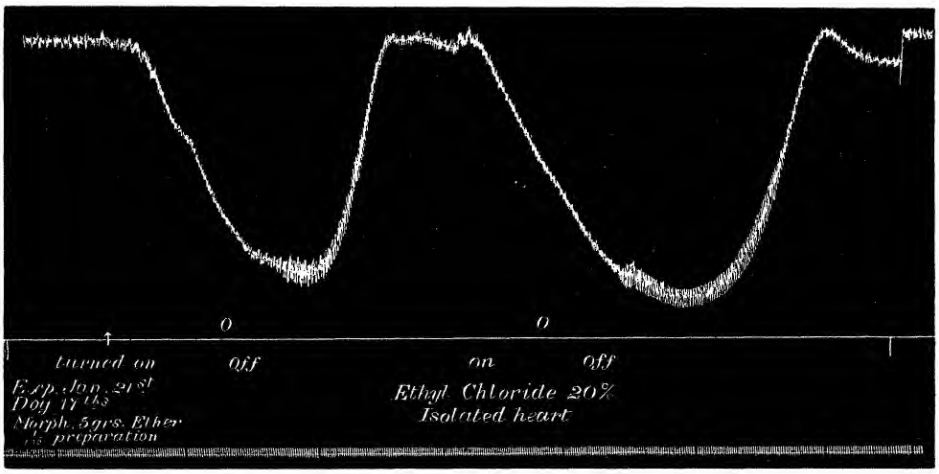

FIG. 3.—$\frac{3}{4}$ size of original.

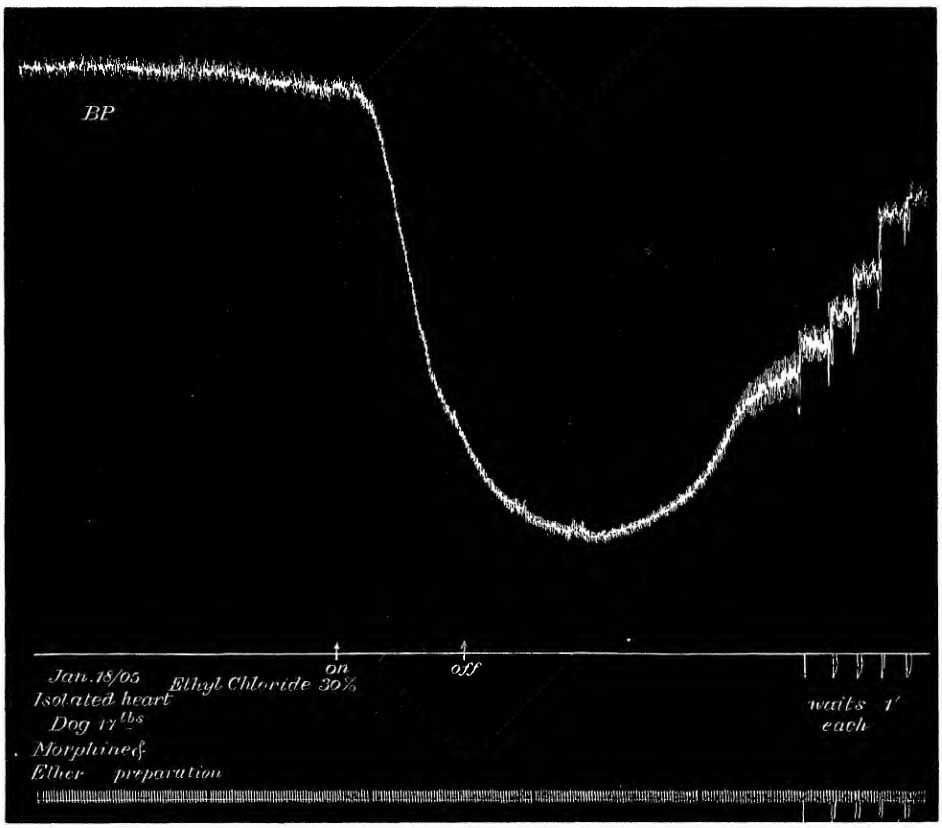

FIG. 4.—$\frac{1}{1}\frac{2}{3}$ size of original.

The heart rate increased in some experiments, but it will be noticed, on reference to the tracings, that in the experiments with stronger mixtures the rate slowed after the administration had been discontinued.

In subsequent experiments on the intact animal, with natural respiration, it appeared impossible to introduce sufficient ethyl chloride into the circulation by inhalation to produce the above rapid paralysis of heart muscle, as cessation of respiration or vagus inhibition of the heart occurred to check further intake.

Conclusions.—The effect of ethyl chloride upon heart muscle, as in the case with chloroform and in contrast with that of ether, is paralytic, but the quantity of ethyl chloride vapour in the air required is 19 times as great as that of chloroform to produce comparable results.

Effect of Ethyl Chloride upon the Vascular System.

This investigation was approached in three ways :—

(1) By investigating the effects of ethyl chloride upon the arterioles independent of the central vaso-motor system.

(2) By investigating its effect upon the central vaso-motor mechanism.

(3) By investigating the resultant of its combined action on the vessels and on the vaso-motor system in the intact animal.

(1) *The Effect of Ethyl Chloride upon the Arterioles.*

This was accomplished by measuring the changes in the outflow, under constant pressure, of blood circulating through a loop of excised bowel together with the isolated lungs of the animal. The method employed was that described, in a similar research in connection with chloroform, by Embley and Martin (6).

After sufficient time had been allowed for the circulatory flow to become constant, air containing 30 per cent. of ethyl chloride vapour was pumped into the lungs. The curve, fig. 5, was plotted from the tracing which recorded the drop-rate, the time, and the pressure. The ordinates represent the number of drops per minute against time in minutes along the abscissæ. The 0 and 8 perpendicular lines indicate the time during which the anæsthetic was administered. The pressure at which the blood circulated was 80 mm. Hg throughout.

The ethyl chloride was administered during 8 minutes, and it will be seen that, following upon the introduction of the ethyl chloride into the respired air, a gradual increase in flow occurred which continued after the administration had ceased. The maximum effect was a 50·5 per cent. increase. This rate

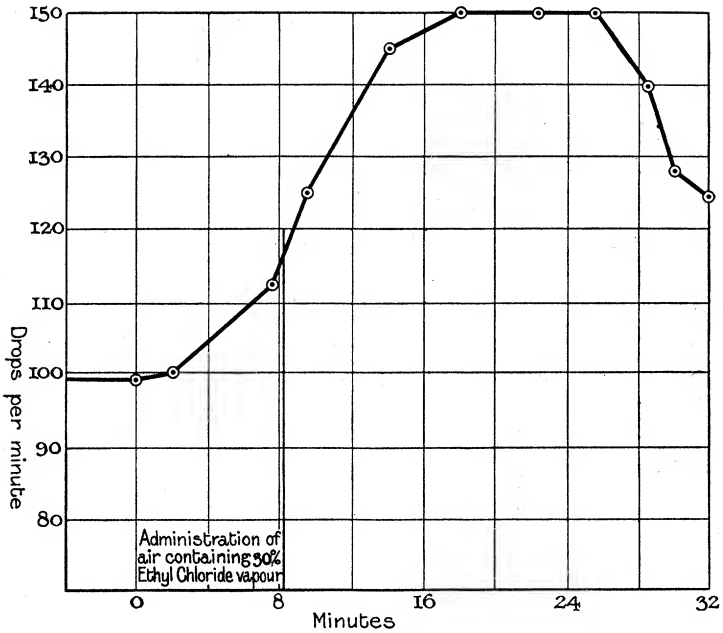

FIG. 5.

of increase was maintained for 7′ 30″, and it was 17′ 30″ after the discontinuance of the ethyl chloride ere it began to diminish.

These experiments demonstrate that the effect of ethyl chloride upon the arterioles isolated from the central nervous system is relaxation. In this respect it is similar to chloroform, but the amount required is vastly greater.

(2) *The Effects of Ethyl Chloride upon the Central Vaso-motor System.*

This was investigated by conveying the ethyl chloride to the brain alone, upon the lines pursued by Gaskell and Shore (7) in their work on chloroform. They employed an extensive proceeding, which consisted in connecting the vessels to and from the brain of one dog with the circulatory system of another and larger dog, so that the larger dog supplied the brain of the other dog. The chloroform was then administered to the larger dog and records taken of each. The brain alone of the smaller dog received chloroform. In the following experiments an artificial arterial circulation replaced that of the large dog of Gaskell and Shore's experiments.

The defibrinated blood of another dog, containing various known percentages of ethyl chloride, was delivered by the artificial arterial circulation apparatus to the brain through the two carotid arteries, for short periods at a time. The temperature of the blood in this artificial supply was 38° C., and the pressure the same as that in the femoral artery

of the dog at the commencement of the experiment. The animal was curarised. Simultaneous records of arterial pressure and bowel volume were taken.

Fig. 6, showing bowel volume (B.V.) and blood-pressure (B.P.), demonstrates the effect of blood saturated with air containing 30 per cent. of ethyl chloride vapour delivered to the brain for 19, 23, and 13 seconds in the first, second, and third delivery respectively. The first effect produced is vaso-constriction as shown by the simultaneous rise in blood-pressure and diminution in bowel volume. After 4′ 15″ the second delivery was made, but the effect produced, although under the same conditions, was the very reverse of the first, for the blood-pressure fell simultaneously with the

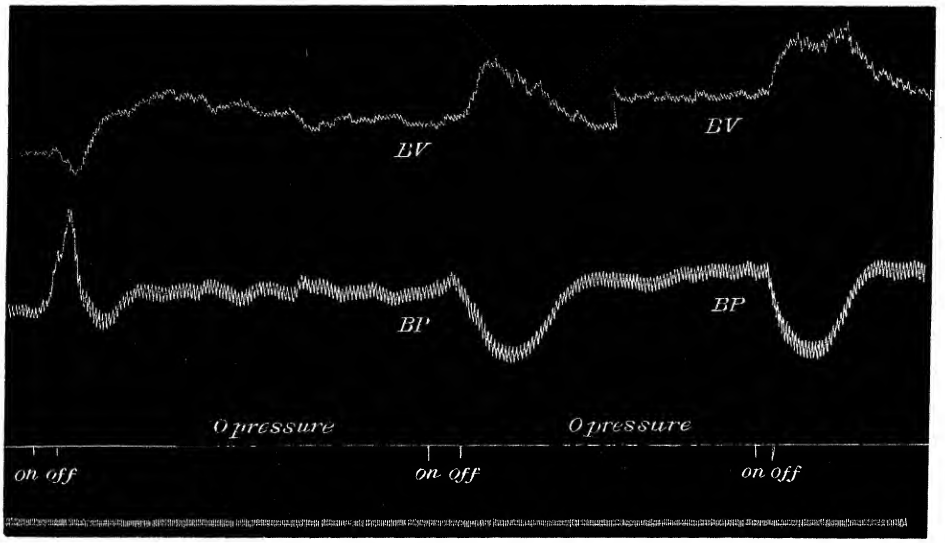

Fig. 6.—½ size of original.

occurrence of an increase in the size of the bowel volume. The third delivery, again under the same conditions, produced effects similar to the second. These latter were obviously vaso-dilator effects.

Further experiments with the same dog produced combinations of these results. At one time vaso-constriction was followed by vaso-dilation in the one delivery. At another delivery vaso-constriction was followed by vaso-dilation, and then by vaso-constriction. In the last experiments the artificial circulation was continued for as long as 40″—much longer than in the former. In similar experiments upon other dogs the constrictor effects were more marked and more prolonged. When lower percentages were used the same results ensued, and the effect was roughly proportional to the concentration of ethyl chloride in the blood injected.

I conclude, therefore, that the effect of ethyl chloride upon the central vaso-motor mechanism, as was shown to be the case for chloroform by Gaskell and Shore (8) and myself (9), is, for a time at least, stimulative.

(3) *The Resultant of the Combination of the Effects of Ethyl Chloride upon Arteriolar Muscle and Vaso-motor System in the Intact Animal.*

This was investigated by taking simultaneous blood-pressure and plethysmographic records during the administration of ethyl chloride. Additional evidence was furnished by vertical rotation of animals under deep ethyl chloride narcosis.

Fig. 7 represents the simultaneous record of blood-pressure and volume of a piece of bowel, following the administration of air containing 30 per cent. of ethyl chloride to an intact dog.

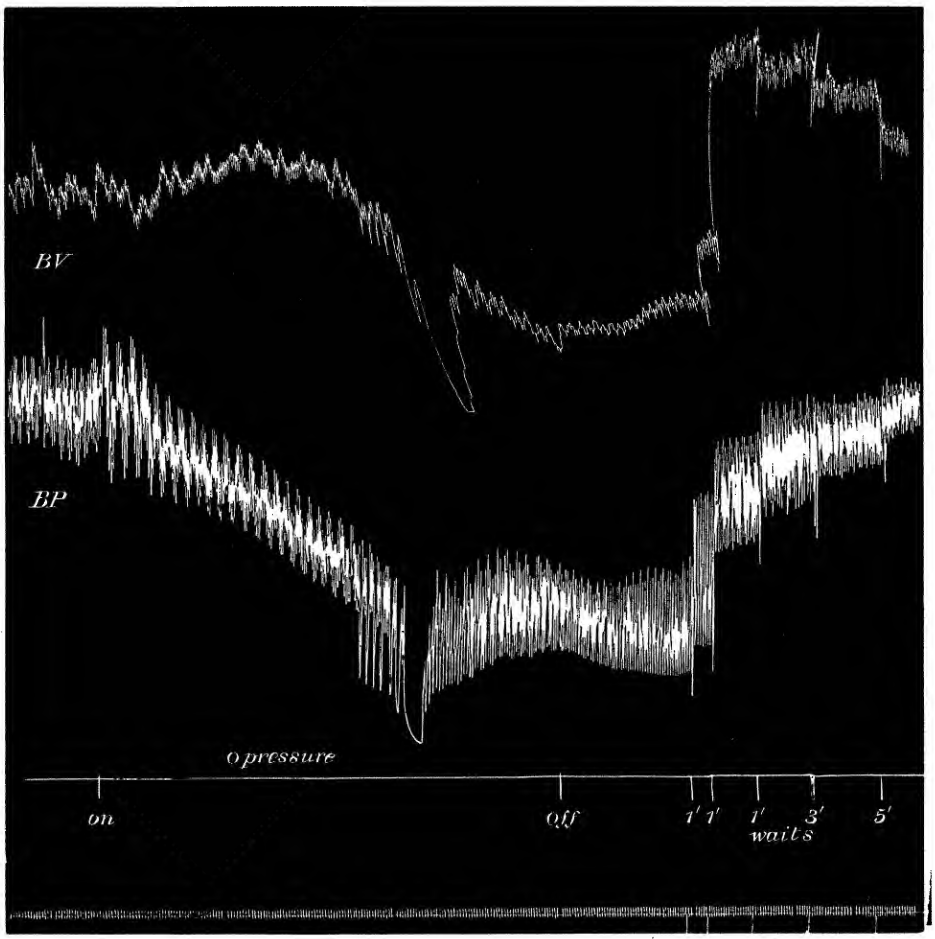

FIG. 7.—$\frac{2}{3}$ size of original.

The administration was continued for 2′ 45″. A preliminary small rise and a simultaneous small diminution in bowel volume occurred, due apparently to vaso-constrictor stimulation. This was followed by a fall in blood-pressure and increase in bowel volume, so that in 1′ 15″ the blood-pressure had fallen 46 mm. Hg, and the tambour lever of the bowel record had risen 5 mm., showing an increase in bowel volume. This increase in bowel volume, however, was not maintained against the concomitant continued fall of blood-pressure, so that the bowel volume soon diminished. The tambour lever in the ensuing 1′ 20″ fell 27 mm., whilst the blood-pressure fell a further 19 mm. After the administration had ceased and recovery had begun, a great increase in bowel volume occurred during the recovering blood-pressure, so that in 3′ 5″ after cessation of administration the lever of the tambour had risen 42 mm., which was 20 mm. above its level before starting the administration of ethyl chloride, whilst the blood-pressure had risen 39 mm. Hg—still 24 mm. below the pressure before starting the ethyl chloride. In 13′ 25″ from cessation of administration of ethyl chloride the blood-pressure and bowel volume had returned to their former levels.

This result is seen, upon comparison, to be precisely similar to those which Martin and I (10) obtained during our investigation of this question in chloroform narcosis. In each the organ volume was found to increase at first for a time, although the blood-pressure was falling, but to soon diminish as the blood-pressure continued to fall and after cessation of the administration to rise above the level that it had previous to commencing the administration, although the blood-pressure still lagged considerably below the height it had previous to the administration of ethyl chloride or chloroform. The interpretation is the same as that given in the chloroform researches above mentioned, and is that the heart recovered before the blood-vessels and poured blood into the relaxed arteries, thereby occasioning a considerably greater increase in the organ volume; and that this condition was maintained until the vessels recovered their tone, when the volume returned to its previous level.

Vertical rotation of the intact animal, with the head up, under deep ethyl chloride anæsthesia induced by artificial respiration, brought down the blood-pressure from 70 to 48 mm. Hg.

The results of vertical rotation under deep ethyl chloride narcosis are considerably less marked than those produced by chloroform. With a corresponding depth of narcosis with chloroform a fall to zero was usually observed. The paralysis of the local vaso-motor mechanism is apparently much less profound in a corresponding depth of anæsthesia with ethyl chloride.

Conclusion.—The net result of the action of ethyl chloride upon the vascular

system, therefore, is dilatation, but the degree of paralysis is strikingly less than that produced by chloroform, even when the latter is present in less than one-tenth the quantity in the air inspired.

The Effect of Ethyl Chloride upon the Vagus Mechanism.

This question was investigated by taking blood-pressure records of the same and different dogs with various percentages of ethyl chloride vapour in the air respired, (a) with intact vagi; and (b) after section of the vagi.

(a) *The Effect of Ethyl Chloride in varying Percentages in the Air inspired* upon the rate of the heart is seen in the table below, which is compiled from a number of experiments with different percentages of ethyl chloride in the air inhaled:—

3·5	p.c. in	15′	caused no change in the heart rate or blood-pressure.					mm. Hg.
7	p.c. in	13′	caused heart rate to fall from	90	to	69	per min. and blood-press. to fall from	127 to 80
10	„	14′ 30″	„	„		65 „ 30	„ „	195 „ 50
10	„	2′ 15″	„	„		86 „ 0	„ „	100 „ 10
15	„	6′ 10″	„	„		74 „ 0	„ „	120 „ 8
20	„	7′ 30″	„	„		90 „ 40	„ „	124 „ 90
30	„	1′ 18″	„	„		80 „ 10	„ „	120 „ 24
30	„	8′ 40″	„	„		84 „ 14	„ „	116 „ 18
30	„	3′ 20″	„	„		86 „ 0	„ „	100 „ 10
30	„	2′ 45″	„	„		90 „ 10	„ „	112 „ 50
30	„	4′ 30″	„	„		88 „ 16	„ „	104 „ 30

Figs. 8, 9, and 10 are blood-pressure curves obtained under the influence

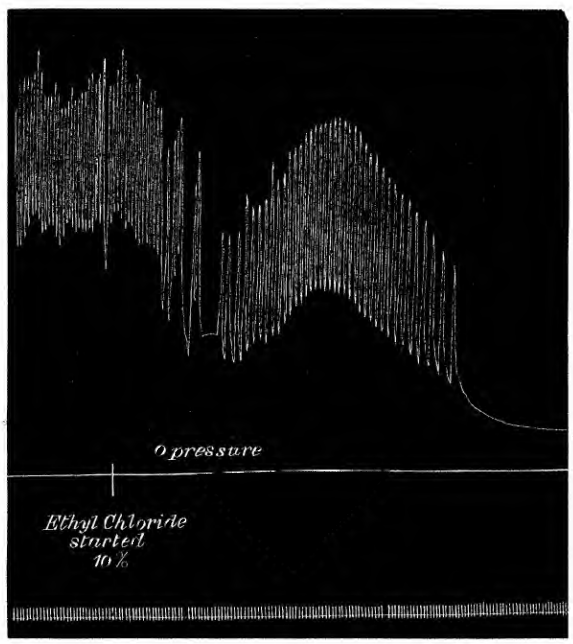

Fig. 8.—Original size.

of 10, 10, and 30 per cent. respectively of ethyl chloride in the air respired. In the above cases the vagi were intact. The varying rapidity of onset of inhibition with the same or different percentages of the anæsthetic denotes variations in the excitability of the vagus mechanism in these experiments.

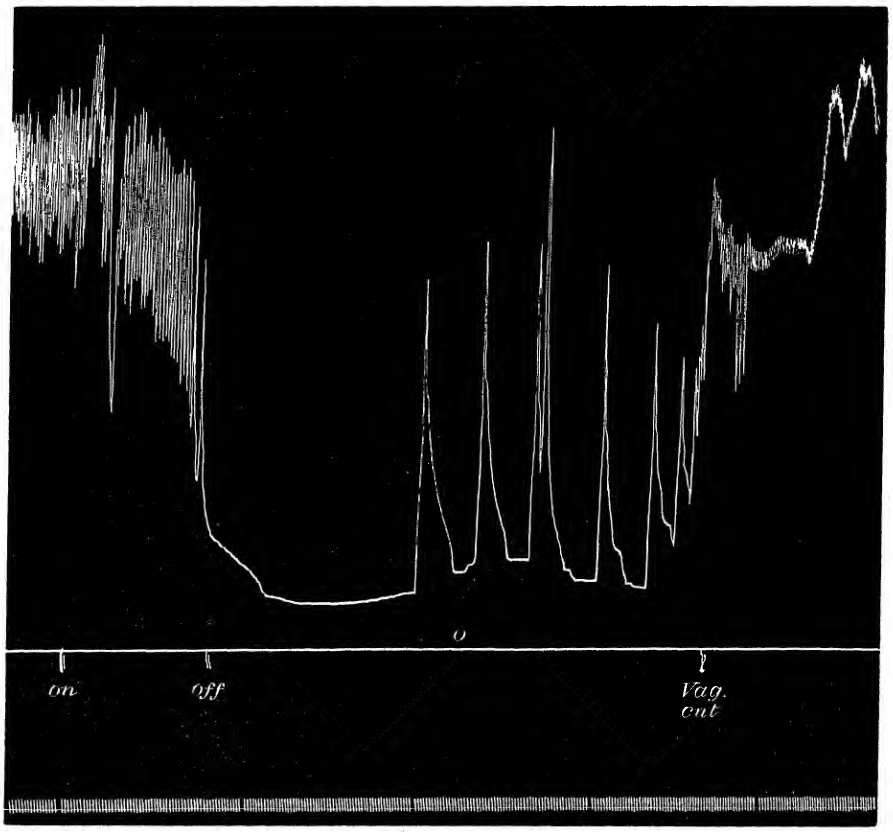

Fig. 9.—Original size.

(b) *The Effect of Ethyl Chloride in varying Percentages upon the Heart Rate after Section of the Vagi* is seen below:—

10 p.c. in 14′ caused no change in heart rate and no fall in blood-pressure.
15 „ 12 „ „ „ „
20 „ 12 „ „ „ „
20 „ 13 „ „ a fall in blood-pressure from 78 to 70 mm. Hg.
30 „ 7 „ „ „ „ „ 102 „ 38 „

The heart rate was altered in none of these experiments. In three out of the five there was no fall in pressure. In the fourth there was a fall, but it was slight. The duration of the administration in these cases was

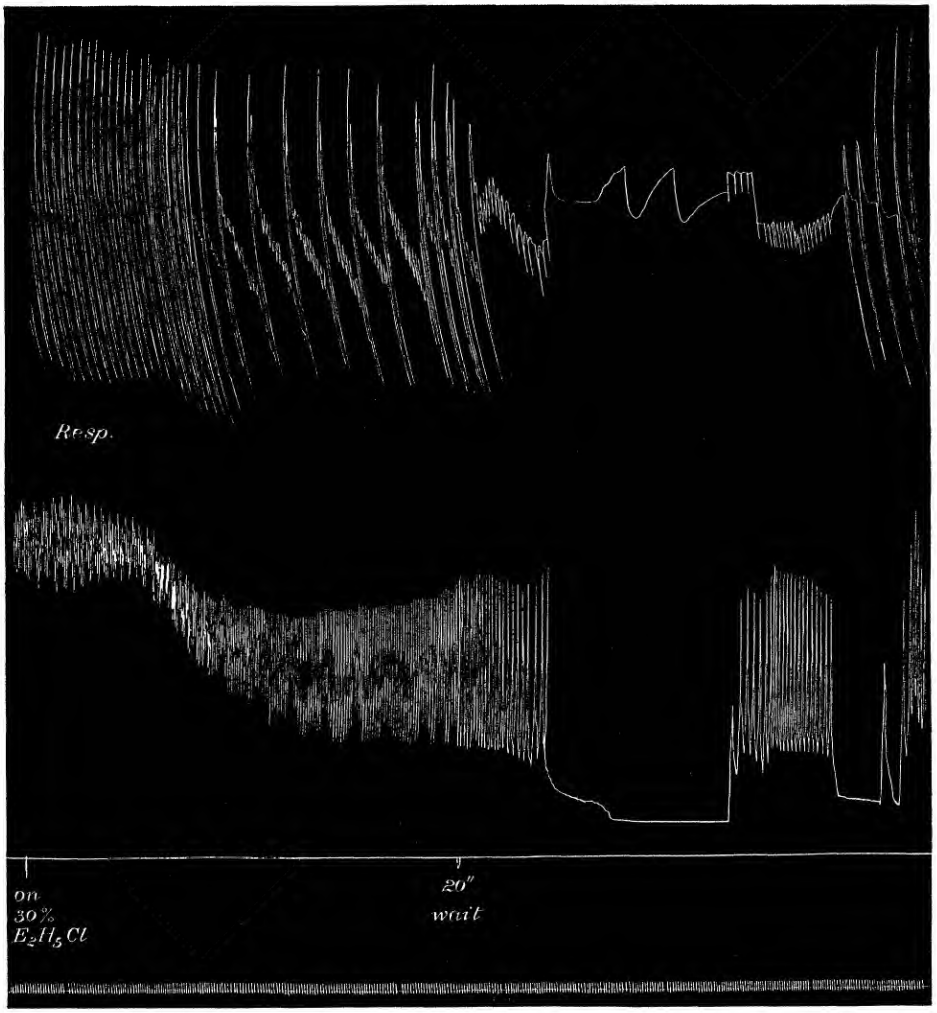

FIG. 10.—$\frac{4}{5}$ size of original.

considerably longer than that of the average (see the former table) required to bring on marked slowing of the heart rate and great fall of blood-pressure. In the fifth experiment (second table), in which 30 per cent. of ethyl chloride was administered in the inspired air, the blood-pressure fell from 102 to 38 mm. Hg in 7′ without alteration in the heart rate. In this experiment the fall of blood-pressure was due to the paralytic effect of the anæsthetic upon the heart and vessels.

From these results it is evident that great and sudden falls of blood-pressure may occur from the administration of ethyl chloride in strength of 10 per cent. and upwards, and that when the strength of the vapour does not

exceed 20 per cent. in the air inspired the slowing of the heart rate from vagus inhibition is the cause of that fall. When a strength of vapour of 30 per cent. and upwards is administered the fall of blood-pressure is in part due to cardio-vascular paralysis, but a fall of blood-pressure occurring without slowing of the heart rate is due wholly to cardio-vascular paralysis.

These statements apply to dogs. They, moreover, apply for short periods—not more than 14′ periods, which, however, are longer than those during which ethyl chloride is generally used in clinical administrations.

In comparing the cases of inhibition of the heart produced by chloroform in my previous experimental work (11), I find that 2·5 per cent. chloroform vapour in the air administered produces approximately the same degree of cardiac inhibition as 10 per cent. ethyl chloride.

There is, however, a difference of vast clinical interest between the inhibition produced by chloroform and that by ethyl chloride, since inhibition due to chloroform is liable to prove fatal, whereas I have not succeeded, in this investigation, in causing a fatal case of cardiac inhibition with ethyl chloride. Furthermore, I have never succeeded in fatally arresting the heart by faradic stimulation of the peripheral ends of the divided vagi under any depth of ethyl chloride narcosis. Whereas, with chloroform, faradic stimulation under like conditions and deep degree of narcosis easily brought about this result (11).

If, however, we compare the results of chloroform (5) and of ethyl chloride upon the heart alone (p. 393), and upon the vagus mechanism alone, it is seen that whilst it requires approximately (p. 401) four times more ethyl chloride to produce the same degree of inhibition as is produced by chloroform in a given time, it requires approximately 19 (p. 396) times as much ethyl chloride to produce the same degree of cardiac depression in the same period of time as is produced by chloroform. Hence it is that in these experiments cardiac inhibition has come on early—before the spontaneous excitability of the heart has been much depressed. Herein, therefore, appears to lie the reason why 30 per cent. and upwards of ethyl chloride vapour in the air inspired has not produced fatal cardiac inhibition in the experiments with ethyl chloride. Herein, too, lies the cause of the relative safety of ethyl chloride.

That the slowing of the heart under the influence of ethyl chloride is due to vagus inhibition is proved by its prompt cessation upon section of these nerves, as is shown in fig. 9. This experiment also proves that the inhibition is not a reflex arising from stimulation of the sensory nerve ends in the mucous membrane of the nose, trachea, or bronchi, or in the alveoli of the lungs, but to direct central stimulation, for in this experiment defibrinated blood

saturated with air containing 30 per cent. of ethyl chloride vapour was delivered to the brain as an independent arterial circulation, as described above (p. 397). Inhibition occurring in these experiments, in which no ethyl chloride comes into contact with the respiratory tract or the alveoli, must necessarily be central. The inhibitory action of ethyl chloride is thus similar to that of chloroform, and due to the direct action of the drug upon the vagus mechanism in the medulla.

Conclusions Regarding the Effect of Ethyl Chloride upon the Vagus Mechanism.

(1) Vagus inhibition of the heart occurs very readily when ethyl chloride vapour of a strength of 10 per cent. and upwards is administered in the air inspired.

(2) Sudden fall of blood-pressure occurring during the administration of ethyl chloride vapour in the air inspired ranging in strength from 10 per cent. to 20 per cent. is due to vagus inhibition of the heart. During the administration of 30 per cent. or upwards the fall of pressure is also due to weakening of the cardiac and arterial musculature.

(3) Cardiac inhibition is not so serious from ethyl chloride as it is from chloroform, since it comes on before the spontaneous excitability of the heart has been much depressed. It does not seem possible to permanently arrest a dog's sound heart under ethyl chloride narcosis by vagus inhibition. It requires 19 times more ethyl chloride to produce a given degree of cardiac depression than is required of chloroform, whilst it requires only four times as much to produce cardiac arrest by vagal stimulation, hence inhibition sets in relatively rapidly. Herein lies the relative safety of ethyl chloride.

(4) The cardiac inhibition arises from central stimulation. It is not reflex.

(5) No evidence of any paralysis of vagus endings, such as was described by Cole, was obtained.

Inter-dependence of Blood-pressure and Respiration.

The investigation of this subject in chloroform narcosis demonstrated (12) that the integrity of the nervous mechanism of respiration was dependent upon the maintenance of blood-pressure. When the blood-pressure fell below a certain level the respiration failed and recovered when the blood-pressure rose again. In the present investigation of this subject in ethyl chloride narcosis, simultaneous tracings were taken of the blood-pressure and respiration with varying percentages of ethyl chloride vapour in the air inspired and the results compared with those of chloroform mentioned above.

The following table gives some of the results taken from 35 experiments performed in this connection.

3—5	p.c. C_2H_5Cl	vapour	in air	inspired. Respiration unaffected.
7	,,	,,	,,	,, in 13′.
10	,,	,,	,,	slowed in 14′.
10	,,	,,	,,	arrested in 2′ 15″. Blood-press. at 10 mm. Hg from cardiac inhibition.
15	,,	,,	,,	arrested in 5′ 40″. Blood-press. at 40 mm. Hg from cardiac inhibition.
18·5	,,	,,	,,	arrested in 8′ 10″. Blood-press. at 20 mm. Hg from cardiac inhibition.
20	,,	,,	,,	greatly slowed. Blood-press. at 68 mm. Hg from cardiac inhibition.
20	,,	,,	,,	arrested in 5′ 35″. Blood-press. at 56 mm. Hg from cardiac inhibition.
30	,,	,,	,,	arrested in 3′ 10″. Blood-press. at 15 mm. Hg from cardiac inhibition.
30	,,	,,	,,	greatly slowed in 8′ 40″. Blood-press. at 18 mm. Hg from cardiac inhibition.
30	,,	,,	,,	arrested in 3′ 14″. Blood-press. at 35·5 mm. Hg from cardiac inhibition.
30	,,	,,	,,	arrested in 2′ 45″. Blood-press. at 50 mm. Hg from cardiac inhibition.

In each of these experiments the respiration returned as the blood-pressure recovered.

It was found, as this table shows, that the blood-pressure falls considerably before the respiration stops, which latter recovers when the blood-pressure rises again, as in fig. 10. The correspondence with the effects of chloroform is still closer, since respiration may be paralysed by ethyl chloride independently of fall of blood-pressure, but not under the ordinary conditions of administration by respiration. It occurs, for instance, when, the liquid ethyl chloride is sprayed into the pharynx, but then only when the vagi are cut or in a state of depressed excitability, otherwise inhibition of the heart would occur and a fall of blood-pressure ensue in consequence.

There is, however, a type of respiration which seems peculiar to a certain depth of ethyl chloride narcosis. It is found to occur as an antecedent to respiratory failure. It is characterised by a remarkable prolongation of the respiratory pause. The tracing closely resembles that which occurs after division of the vagi in an otherwise normal dog, but with the difference that in this case the vagi are unsevered, as is seen in the blood-pressure tracing, fig. 11, in which the successive respirations occur at the apex of each curve. The blood-pressure falls after each small group of inspirations in consequence of the slowing of the heart rate itself, a result of vagus inhibition. The further accession of ethyl chloride to the blood stream being prevented by the arrest of further respiratory intake, stimulation of the vagus mechanism

passes off, the heart's rate increases and the blood-pressure rises to its former level. Another set of respirations is then taken and the same cycle of events follows. In this manner respiratory arrest is delayed. The animal is, however, becoming asphyxiated, so that either the heart must be arrested by the consequent exalted irritability of the vagi or the respiration cease. One of these occurrences is found by experiment to occur. This form of respiration does not always precede respiratory failure. It occurs generally when excessively large percentages of ethyl chloride are administered in the air.

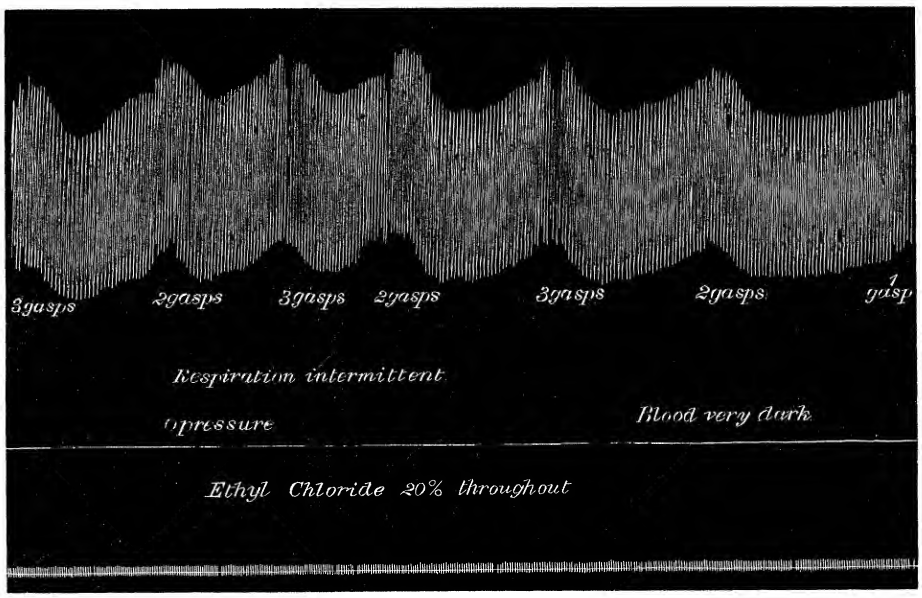

FIG. 11.—$\frac{3}{4}$ size of original.

In some experiments respiration failed independently of a fall in blood-pressure. In this case the respiration may remain in abeyance for considerable periods (6′ to 7′) without the blood-pressure being depressed, and subsequently continue in a normal manner.

The comparison of these results with those of chloroform (12) indicates that 10 per cent. of ethyl chloride vapour produces approximately the same effects upon the respiration as 2·5 per cent. of chloroform vapour in the air inspired. This quantitative relation is about the same as that which was found to obtain in the case of stimulation of the vagus mechanism by these two agents (p. 401).

In none of these experiments was it found that the heart was arrested before the respiration. Since, however, slowing of the heart usually began before the respiration showed signs of stoppage, it is possible that the heart

In the following table are collected a few observations upon the heart rate, respiration, blood-pressure, and corneal reflex from experiments with varying but known percentages of ethyl chloride in the air respired by natural respiration (except in one case):—

Dose.	Vagus inhibition of heart.	Respiration.	Fall of blood-pressure in mm. Hg.	Heart rate per minute.	Corneal reflex abolished.
Per cent.					
3·5	None in 15′	Unaffected in 15′	None in 15′	Unaffected in 15′	None in 15′
7	Slowing only	Unaffected in 13′	127 to 80 in 13′	90 to 69 in 13′	Gone in 2′ 4″
10	None	Slowing	Unaffected in 14′	Unaffected in 14′	,, 1′ 45″
10	Slowing only	Little irregular	198 to 50 in 14′ 30″	65 to 30 in 14′ 30″	,, 1′ 30″
10	Slowing down to arrest	Ceased as heart ceased	100 to 0 in 2′ 15″	60 to 0 in 2′ 15″	,, 1′ 30″
15	None	Unimpaired	Unaffected in 12′	Unaffected in 12′	,, 1′ 45″
15	Slowing down to arrest	Ceased twice for 2′ each	120 to 8	Slowing to stop, 74 to 0	,, 1′ 30″
18·5	,, ,,	Ceased in 8′ 10″	120 to 0 in 8′ 25″	65 to 0 in 8′ 25″	,, 1′ 15″
18·5	Slowing intermittently	Very slow	Unaffected in 14′	Intermittent rise and fall	,, 1′ 15″
20	,, ,,	,,	Falling after one inspiration, rising before the next	,, ,,	,, 1′ 30″
20	None	,,	78 to 70 in 13′	Unaffected in 13′	,, 1′ 45″
20	,,	Unimpaired	Unaffected in 12′	Unaffected in 12′	,, 1′ 10″
20	Slowing only	,,	124 to 90 in 7′ 30″	90 to 40 in 7′ 30″	,, 1′ 0″
20	Slowing	Ceased in 5′ 35″	135 to 56	68 to 24	,, 1′ 15″
30	Great slowing	Failed in 1′ 15″	120 to 24 in 1′ 15″	80 to 10 in 1′ 15″	,, 0′ 45″
30	Slowing intermittently	Very intermittent	116 to 18 in 8′ 40″	84 to 14 in 8′ 40″	,, 1′ 15″
30	Slowing down to arrest	Ceased at 0 blood-pressure	100 to 10 in 3′ 20″	86 to 0 in 3′ 20″	,, 0′ 35″
30	None	Unimpaired	102 to 38 in 7′	Unaffected	,, 1′ 10″
30	Great slowing	Failed in 2′ 45″	112 to 50 in 2′ 45″	90 to 10 in 2′ 45″	,, 0′ 50″
30	Arrested	Failed in 3′ 14″	124 to 0	80 to 0	,, 0′ 55″
30	Great slowing	Artificial respiration	104 to 30 in 4′ 30″	88 to 16 in 4′ 30″	,, 0′ 40″

may, in some instances in which there is exalted vagus irritability, stop before the respiration.

Conclusions.—In ethyl chloride narcosis the integrity of the respiratory mechanism is dependent upon the maintenance of blood-pressure.

Paralysis of respiration may be preceded by shallow respiratory movements, but it is usually preceded by deep and delayed breaths, and in some cases the prolonged pause between the expiration and the following inspiration prevents the fall of blood-pressure.

In all of the experiments performed the respiration failed before the heart.

Conclusions.

Conclusions with Regard to the Effects of Ethyl Chloride on Dogs.

(1) Quantities above 9 per cent. of ethyl chloride in the air respired exert a paralytic effect upon heart muscle similar to that produced by chloroform in $\frac{1}{19}$th the concentration.

(2) The central vaso-motor system is at first stimulated, and the peripheral mechanism of the arterioles is paralysed. The local paralytic effect is more significant than the central stimulation, so that the sum of these opposing factors is relaxation. This result is similar to that produced by chloroform, but the effect is never so profound, and requires for its production much higher concentration of ethyl chloride vapour.

(3) Its effect upon the vagus system is one of stimulation, and with high concentration the heart is readily arrested by vagus inhibition. As, however, the spontaneous excitability of the heart muscle is not seriously impaired, the heart escapes from vagus inhibition, and in no case has death occurred from this cause. To produce the same inhibitory effect with chloroform requires approximately a quarter the concentration in the respired air. Since it requires $\frac{1}{19}$th the concentration of chloroform to produce the same paralytic effect upon heart muscle, inhibition from ethyl chloride must ensue a variable period before the spontaneous excitability of the heart muscle is seriously impaired.

It is on this difference between the action of the two anæsthetics that the relative safety of ethyl chloride rests. The vagus system is not so readily depressed by prolonged administration as is the case with chloroform.

(4) Like chloroform the respiration under ethyl chloride narcosis is dependent upon the maintenance of the blood-pressure. The cause of the fall of blood-pressure from ethyl chloride is mainly vagus inhibition, whereas that from chloroform is cardiac paralysis completed by inhibition. Respiratory failure occurring apart from fall of blood-pressure, as, for

instance, in experiments with vagi cut, occurs within 15′ when the concentration of ethyl chloride exceeds 20 per cent.

In administrations not exceeding 15′ duration (these statements do not hold for periods exceeding this) in addition to the above-mentioned effect on the blood-pressure brought on through the vagus mechanism, the pressure falls from paralysis of the cardiac muscle when the concentration exceeds 20 per cent. The rate of fall of blood-pressure always varies with the rate of the respiration.

(5) 5 to 7 per cent. of ethyl chloride vapour in the air respired appears to be the limit of safety from syncope in dogs for prolonged and continuous administration. If this concentration be exceeded, it is inadvisable to continue the administration beyond abolition of the corneal reflex, otherwise syncope is very probable.

These conclusions with regard to the effects of ethyl chloride upon dogs likely apply to man. In man I have observed syncope occur in two instances and recovery to take place with a sudden return of pulse of fair volume and sudden replacement of the colour of death by that of life. From analogy with experimental results I regard such syncope as due to vagus inhibition. These conclusions, however, cannot be expected to hold good in clinical instances of failing heart and other morbid states that may embarrass recovery. A sound heart is able to free itself from vagus arrest, but the degree of depression caused by ethyl chloride may be sufficient during the period of syncope to embarrass an unsound heart beyond recovery.

To employ a gasometer with the ethyl chloride vapour mixed with air in the proportions required by the anæsthetist would be the most rational method of administration. The necessity of carrying a large bag for this purpose would, however, rob this anæsthetic to some extent of one of its advantages, viz., portability. The administration is rendered less safe by the employment of any apparatus for its administration in which the anæsthetic is sprayed or poured into the instrument between the face piece and the bag, so that during inspiration excessively high degrees of concentration of ethyl chloride vapour may be given. The anæsthetic should at least be allowed to mix with the air by being introduced at the end of the bag.

I acknowledge with much gratitude my indebtedness to Professor Osborne for his generous hospitality and assistance and for the use of his laboratory during the course of this investigation.

[*Note by Dr. C. J. Martin.*—Since Dr. Embley's paper was communicated

to the Society, an investigation into the action of ethyl chloride, by Webster, has appeared in the 'Bio-Chemical Journal,' June, 1906, vol. 1, p. 328.

In Webster's experiments, as in Cole's, the quantity of ethyl chloride administered was not determined. This observer concludes that—(1) after a preliminary increase, the respiration rapidly diminished in rate and extent; (2) after a preliminary slight rise, the blood-pressure fell; (3) no paralysis of vagus endings occurs (in contradiction to Cole); (4) the action upon the circulatory system is, almost entirely, directly upon the heart.

Some of the records illustrating Webster's paper show marked vagus inhibition occurring during the course of the administration of the anæsthetic, but the author does not remark upon this fact.]

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EXPLANATION OF FIGURES.

FIG. 1 ($\frac{3}{4}$ size of original).—Isolated heart. Recovery. Dog. Weight, 8 kilogrammes. Morphine, 0·3 gramme and ether for anæsthesia in preparation. Common trunk of right carotid and subclavian arteries ligatured. The left carotid used for the monometer, and the aorta tied just beyond the left subclavian. The left subclavian artery is thus left open to carry the circulation. Its ascending branches and the vertebral arteries are then ligatured. Vagi cut. Artificial respiration. Blood-pressure tracing. Blood-pressure at starting 92 mm. Hg, 10 per cent. ethyl chloride vapour in the inspired air at starting "on" continued for 8′ 15″ and stopped at "off." The blood-pressure fell to 58 mm. The blood-pressure rose to 104 mm. in 9′ 35″ after administration ceased.

FIG. 2 ($\frac{3}{4}$ size of original).—Isolated heart. Recovery. Dog. Weight, 8·5 kilogrammes. Morphia, 35 grammes and ether for preparation as for experiment in fig. 1. Blood-pressure 158 mm. Hg at starting. Fifteen per cent. ethyl chloride vapour in the air respired started at "on" and continued for 3′ 12″ and stopped at "off." Blood pressure fell to 63 mm. Hg. In 2′ 12″ the blood-pressure had returned to 139 mm.

FIG. 3 ($\frac{3}{4}$ size of original).—Isolated heart. Recovery. Dog. Weight, 7·7 kilogrammes. Morphine, 0·32 gramme. Experiment similar to that of fig. 1, but 20 per cent. ethyl chloride was used in the air respired. Two experiments were performed. Started at "on" and stopped at "off" after 61″. Blood-pressure at start was 160 mm. Hg and fell to 70 in 1′ 30″. It recovered to 160 mm. in 1′ 25″ after stopping the administration. In 33″ after the recovery the administration was again started at the second "on" and continued for 59″. During that time the blood-pressure fell from 160 mm., reaching 62 mm. in 1′ 35″. It rose to 162 after administration ceased in 1′ 50″.

FIG. 4 ($\frac{12}{13}$ size of original).—Isolated heart. Recovery. Dog. Weight, 7·7 kilogrammes. Morphine, 0·32 gramme. Preparation as for experiment in fig. 1. Thirty per cent. ethyl chloride vapour in the respired air started at "on" and continued 46″. Blood-pressure, 164 mm. before starting, fell to 34 mm. in 1′ 34″. In 2′ 49″ it had risen again to 134 mm. Hg.

FIG. 5.—Double artificial circulation. Graphic representation of rate of blood flow through a piece of isolated bowel and isolated lungs. Defibrinated blood was circulated; 30 per cent. ethyl chloride vapour in the air was administered by artificial respiration to the isolated lungs. The curve plotted shows the increase of blood flow through the bowel circuit when the ethyl chloride was started.

FIG. 6 ($\frac{1}{2}$ size of original).—Effects of ethyl chloride upon the central nervous system. Bowel volume (B.V.) and blood-pressure (B.P.) figure. Dog, 8·4 kilogrammes in weight. Morphine, 0·3 gramme. Curare, 0·017 gramme. Vagi cut. Artificial respiration. Artificial arterial circulation to the brain, of defibrinated blood of another dog, containing ethyl chloride equal to 30 per cent. of vapour and at 38° C. The pressure was at that of the dog's femoral artery previous to the experiment. It was delivered by way of the two carotid arteries for periods of 19″, 23″, and 13″ in three successive experiments. In the first experiment the blood-pressure rose 57 mm., whilst at the same time the plethysmograph lever fell 6·5 mm. in the 19″ occupied by this artificial delivery. In the second experiment the blood-pressure fell 88 mm. and the lever rose 15 mm. In the third experiment the blood-pressure fell 40 mm. and the lever rose 27 mm. The first result was a constrictor, and the second and third were dilator effects.

FIG. 7 ($\frac{6}{7}$ size of original).—Organ volume measurements. Simultaneous measurements of bowel volume changes (B.V.) and blood-pressure (B.P.). Dog. Weight, 9 kilogrammes. Morphia, 0·4 gramme. Artificial respiration. Air containing 30 per cent. of ethyl chloride vapour administered between "off" and "on" for a space of 2′ 45″. A preliminary small rise of blood-pressure and fall of lever of the oncometer occurred. This was followed by a fall of blood-pressure and a rise in the lever of the oncometer, so that at 1′ 15″ the blood-pressure had fallen 46 and the tambour lever had risen 5 mm. But as the blood-pressure continued to fall the rise in the lever was not maintained and it began to fall, so that when the administration ceased the blood-pressure had fallen 65 mm. and the lever was 22 mm. below the lever at starting. In 3′ 5″ after cessation of administration the tambour lever had risen 42 mm., but the blood-pressure had only recovered 39 mm. The bowel volume was greater than it was before starting, although the blood-pressure was less. The bowel volume and blood-pressure were at their former levels in 13′ 25″.

FIG. 8 (size of original).—Vagus inhibition. Dog. Weight, 4·2 kilogrammes. Morphine, 0·2 gramme. Blood-pressure tracing. Air containing 10 per cent. of ethyl chloride vapour administered by artificial respiration. Blood-pressure at starting 83 mm. After 1′ 45″ administration the blood-pressure fell to 10 mm. from vagus inhibition. Recovery.

FIG. 9 (size of original).—Vagus inhibition from central stimulation. Dog. Weight, 9·4 kilogrammes. Morphine, 0·4 gramme. Curare, 0·02 gramme. Artificial respiration. Artificial arterial brain circulation prepared as in experiment for fig. 6, but with the vagi intact. Blood-pressure figure. Artificially circulating blood contained ethyl chloride equal to 30 per cent. of the vapour. Blood-pressure at starting 126 mm. Artificial circulation started at "on" and continued for 49″, ceasing at "off." Blood-pressure fell to 10 mm. The heart ceased from vagus inhibition. Recovery by vagotomy.

FIG. 10 ($\frac{4}{5}$ size of original).—Interdependence of respiration and blood-pressure. Dog. Weight, 7·8 kilogrammes. Morphine, 0·3 gramme. Respiration (Resp.) and blood-pressure (B.P.) figure. Air containing 30 per cent. ethyl chloride vapour started at "on" and administered continuously. Blood-pressure at starting 103 mm. Hg. In 3′ 54″ the blood-pressure fell to 10 mm. The respiration quickened after the commencement of the administration and slowed with the onset of heart slowing and ceased in 3′ 14″ with blood-pressure 35·5 mm. Hg.

FIG. 11 ($\frac{3}{4}$ size of original).—Respiration and blood-pressure. Dog. Weight, 7 kilogrammes. Morphine, 0·25 gramme. Blood-pressure figure. Ethyl chloride of unknown but large percentage administered by spraying the liquid into the mouth until the respiration ceased. Blood-pressure at starting "on," 118 mm. Some slowing from vagus inhibition occurred after 35″ of administration and lasted 1′ 26″, at which period the respiration, after slowing, ceased. Respiration continued in abeyance for 6′ 56″. Blood-pressure was 99 mm. at cessation of respiration and 98 mm. on its return.